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Original Article

Testosterone Recovery after Neoadjuvant Gonadotropin-Releasing Hormone Antagonist versus Agonist on Permanent Iodine-125 Seed Brachytherapy in Prostate Cancer Patients: A Propensity Score Analysis

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Optimal neoadjuvant hormone therapy (NHT) for reducing prostate cancer (PC) patients' prostate volume pre-brachytherapy is controversial. We evaluated the differential impact of neoadjuvant gonadotropin-releasing hormone (GnRH) antagonist versus agonist on post-brachytherapy testosterone recovery in 112 patients treated pre-brachytherapy with NHT (GnRH antagonist, n = 32; GnRH agonists, n = 80) (Jan. 2007-June 2019). We assessed the effects of patient characteristics and a GnRH analogue on testosterone recovery with logistic regression and a propensity score analysis (PSA). There was no significant difference in the rate of testosterone recovery to normal levels (> 300 ng/dL) between the GnRH antagonist and agonists ($p = 0.07$). The GnRH agonists induced a significantly more rapid testosterone recovery rate at 3 months post-brachytherapy versus the GnRH antagonist ($p < 0.0001$); there was no difference in testosterone recovery at 12 months between the GnRH antagonist/agonists ($p = 0.8$). In the multivariate analysis, no factor was associated with testosterone recovery. In the PSA, older age and higher body mass index (BMI) were significantly associated with longer testosterone recovery. Post-brachytherapy testosterone recovery was quicker with the neoadjuvant GnRH agonists than the antagonist, and the testosterone recovery rate was significantly associated with older age and higher BMI. Long-term follow-ups are needed to determine any differential effects of GnRH analogues on the quality of life of brachytherapy-treated PC patients.

Key words: testosterone recovery, GnRH antagonist, GnRH agonist, brachytherapy, prostate cancer

Permanent brachytherapy is a standard treatment in patients with low- or intermediate-risk prostate cancer [1, 2]. It is often performed in combination with neoadjuvant hormone therapy (NHT) [3]. The European Association of Urology guidelines state that there is no benefit of providing NHT before brachytherapy in terms of oncologic outcomes such as biochemical recurrence-free survival [4]. Similarly, we have reported that NHT did not improve oncologic outcomes in patients with localized prostate cancer and was only successful in reducing the prostate volume (≥ 35 mL) [5].

Testosterone levels usually recover from a castrated level to a normal level after the discontinuation of androgen deprivation therapy (ADT) [6]. However, some patients treated with NHT before brachytherapy

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do not experience persistent testosterone recovery. Low testosterone levels can result in increased risks of cardiovascular diseases (CVDs), diabetes, and osteoporosis [7]. Some studies reported that testosterone therapy did not increase the risks of biochemical recurrence, cancer-specific mortality or overall mortality after surgery or radiation in patients with localized prostate cancer [8, 9]. Tsumura *et al.* investigated the factors predictive of testosterone recovery in patients treated with brachytherapy, and they observed that the duration of hormone therapy was significantly associated with testosterone recovery [10]. On the other hand, Kato *et al.* reported that testosterone recovery after NHT was associated with body mass index (BMI) and hypertension [11]. A recent meta-analysis demonstrated that treatment with a gonadotropin-releasing hormone (GnRH) antagonist was associated with lower rates of musculoskeletal and cardiovascular events such as angina pectoris and myocardial ischemia, compared to GnRH agonists [12, 13].

We hypothesized that a GnRH antagonist might induce earlier testosterone recovery compared to GnRH agonists, and we conducted the present study to investigate the association between the types of GnRH analogue and testosterone recovery.

Patients and Methods

Patient population and management. We analyzed the cases of 132 patients treated with NHT (32 with a GnRH antagonist and 80 with GnRH agonists) before permanent iodine-125 seed brachytherapy at Okayama University Hospital during the period from January 2007 to June 2019. The oral anti-androgen (bicalutamide) was administered according to the treating physician's discretion. Two patients (6%) with a GnRH antagonist and 7 patients (9%) with a GnRH agonist were administered bicalutamide, respectively. We excluded patients treated with other oral anti-androgens and those with a follow-up duration of < 1 year. The risk classification of the patients was performed according to the U.S. National Comprehensive Cancer Network guidelines.

Study protocol. The brachytherapy technique used at our institution has been described [5]; briefly, when the prostate volume is observed by transrectal ultrasonography to be ≥ 35 mL or an adequate dose–volume histogram cannot be determined due to pubic arch interference, NHT is administered for 3 months as a general rule. If the prostate volume is not sufficiently reduced by the NHT, an additional 3-month course of the NHT is administered [5]. In the present patient series, the GnRH antagonist used was degarelix (240 mg initial dose, 80 mg subsequent doses), and the GnRH agonists used were leuprolide (3.75 mg or 11.25 mg) and goserelin (3.6 mg or 10.8 mg). The NHT (GnRH antagonist or agonists) was administered at the discretion of the treating physician without any specific protocol.

We assessed patient age, BMI, histories of hypertension and diabetes mellitus, initial prostate-specific antigen value, pathological stage, Gleason grade group, and the duration of hormone therapy before the patient's brachytherapy. Patients were followed routinely for the measurement of the levels of prostate-specific antigen and serum testosterone every 3 months during the first year, every 6 months during the subsequent 4 years, and annually thereafter. A normal serum testosterone level (testosterone recovery) was defined as ≥ 300 ng/dL, according to the American Urological Association guidelines [14].

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Okayama University Ethics Committee Institutional Review Board (approval no. 2011-015).

Statistical analyses. The Mann–Whitney *U*-test and Fisher's exact test were used to assess the statistical significance of differences in medians and proportions between groups, respectively. The follow-up duration was calculated from the date of the patient's brachytherapy. The Kaplan–Meier estimate was used to evaluate the cumulative rate of testosterone recovery. Gray's test was used to evaluate differences in testosterone recovery according to the types of GnRH analogue. A logistic regression model including age, BMI, histories of hypertension and diabetes mellitus, and combination of anti-androgen treatments was used to calculate propensity scores. A one-to-one pair matching without replacement was performed by the nearest-neighbor matching method with a 0.2 caliper. We performed a univariate logistic regression analysis to identify the factors predictive of testosterone recovery. Variables with $p < 0.05$ in the univariate analysis, as well as the GnRH analogue type (antagonist vs. agonist), were evaluated in the multivariate analysis. Statistical significance was set at $p < 0.05$, and all tests were two-

sided. All statistical analyses were performed using EZR ver. 1.36 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R [15].

Results

There was no significant difference in age, BMI, initial PSA level, history of hypertension or diabetes mellitus, rates of combination with an anti-androgen, or the duration of ADT between the patients who received a GnRH antagonist and those who received GnRH agonists. The group of patients treated with a GnRH antagonist showed significantly more advanced pathological T stages ($p<0.0001$) and included significantly more intermediate-risk patients ($p=0.04$) compared to the patients in the agonist group (Table 1).

Prostate volume reduction. Figure 1 illustrates the reductions in prostate volume after NHT in the GnRH antagonist and agonists groups. The prostate volume before NHT was significantly greater in the patients treated with a GnRH antagonist compared to

Table 1 Patient baseline demographic and pathological characteristics according to gonadotropin-releasing hormone analogue type in full sample and propensity score matched cohort.

	Full sample			Propensity score match		
	Antagonist	Agonist	*P*-value	Antagonist	Agonist	*P*-value
Number of patients	32	80		32	32	
Age (years), median (IQR)	69 (65–72)	68 (64–70)	0.3	69 (65–78)	69 (66–70)	0.6
BMI (kg/m^2), median (IQR)	24 (22–26)	24 (21–26)	0.2	24 (22–26)	25 (23–26)	0.4
Initial PSA level (ng/mL), median (IQR)	7.7 (5.3–12.9)	7.3 (5.4–9.6)	0.2	7.7 (5.3–12.9)	7.6 (5.7–11.1)	0.6
Pathological T stage			<0.0001			<0.0001
T1c, n (%)	11 (34)	60 (75)		11 (34)	27 (84)	
T2a, n (%)	17 (53)	14 (18)		17 (53)	3 (9)	
T2b, n (%)	0 (0)	4 (5)		0 (0)	2 (6)	
T2c, n (%)	4 (13)	2 (2)		4 (13)	0 (0)	
Gleason grade group			0.2			0.2
1, n (%)	18 (56)	58 (73)		18 (56)	24 (75)	
2, n (%)	14 (44)	21 (26)		14 (44)	8 (25)	
3, n (%)	0 (0)	1 (1)				
NCCN risk group			0.04			0.1
Low, n (%)	9 (28)	41 (51)		9 (28)	16 (50)	
Intermediate, n (%)	23 (72)	39 (49)		23 (72)	16 (50)	
Hypertension, n (%)	15 (47)	27 (34)	0.2	15 (47)	14 (44)	1
Diabetes mellitus, n (%)	4 (13)	11 (14)	1	4 (13)	2 (6)	0.7
Combination with anti-androgen, n (%)	2 (6)	7 (9)	1	2 (6)	4 (13)	0.7
Duration of ADT, median (IQR)	3 (3–3)	3 (3–3)	0.1	3 (3–4)	3 (3–3)	0.2
<3 months, n (%)	25 (78)	66 (83)		25 (78)	23 (72)	
>3 months, n (%)	7 (22)	14 (17)		7 (22)	9 (28)	

ADT, androgen deprivation therapy; BMI, body mass index; NCCN, national comprehensive cancer network; PSA, prostate specific antigen.

those treated with GnRH agonists ($p=0.008$), but there was no significant difference between the groups after NHT ($p=0.4$). There was no significant difference in prostate volume reduction between the patients treated with the two GnRH agonists (leuprolide vs. goserelin) (data not shown).

Testosterone recovery. The patients' testosterone recovery rates are shown in Table 2. The rates of recovery to normal testosterone levels in the GnRH antagonist versus agonist groups were 9% (3/32 patients) vs. 55% (40/73) at 3 months, 44% (14/32) vs. 64% (50/78) at 6 months, 63% (20/32) vs. 73% (58/80) at 9 months, and 72% (23/32) vs. 75% (60/80) at 12 months after brachytherapy, respectively. Interestingly, the GnRH agonists induced significantly more rapid testosterone recovery rate at 3 months after brachytherapy compared to the GnRH antagonist ($p<0.0001$), but there was no significant difference in testosterone recovery at 12 months ($p=0.8$) after brachytherapy between the GnRH antagonist and agonist groups. In the multivariate analysis, no factor was associated with testosterone recovery (Table 3). There was no significant difference in the testosterone recovery rates between the GnRH agonists (leuprolide vs. goserelin) (data not shown).

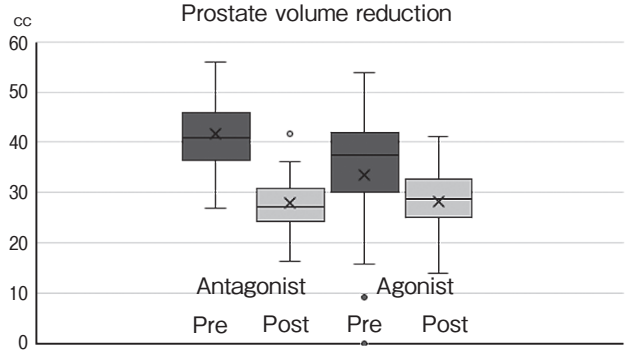

Fig. 1 Prostate volume reduction after treatment with a gonadotropin-releasing hormone (GnRH) antagonist or agonists. Pre, pre-treatment of neoadjuvant hormone therapy (NHT); Post, post-treatment of NHT.

Propensity score analysis. The testosterone level is affected by age, BMI, history of hypertension, history of diabetes mellitus, and anti-androgen therapy [16]. We thus performed propensity score matching of the two groups using these covariates. The patient characteristics of the propensity score-matched cohorts are given in Table 1. In the Kaplan–Meier estimate, there was no significant difference in testosterone recovery rates between the GnRH antagonist and agonist groups ($p=0.07$) (Fig. 2), with a significant difference in the testosterone recovery rate between the two groups seen at 3 months after brachytherapy ($p<0.0001$) (Table 2). In the multivariate analysis performed after propensity score matching, older age and higher BMI were significantly associated with longer testosterone recovery (Table 3).

Discussion

With the increasing interest in focal therapy for prostate cancer, brachytherapy was introduced in Japan in 2003, and more than 43,000 patients have undergone brachytherapy in Japan since then [1]. The impact of NHT on prostate cancer prior to brachytherapy is still controversial. The NHT agent (*e.g.*, GnRH antagonists and agonists) and duration should be considered in the decision whether to perform NHT. At our institution, when the prostate volume is ≥35 mL or an adequate

Table 2 Testosterone recovery rates at different time points after brachytherapy according to type of gonadotropin-releasing hormone analogue in full sample and propensity score matched cohort

	Full sample			Propensity score match		
	Antagonist	Agonist	*P*-value	Antagonist	Agonist	*P*-value
Number of patients	32	80		32	32	
Testosterone recovery rates						
3 month, n (%)	3/32 (9)	40/73 (55)	<0.0001	3/32 (9)	17/28 (61)	<0.0001
6 month, n (%)	14/32 (44)	50/78 (64)	0.058	14/32 (44)	22/31 (71)	0.042
9 month, n (%)	20/32 (63)	58/80 (73)	0.4	20/32 (63)	23/32 (72)	0.6
12 month, n (%)	23/32 (72)	60/80 (75)	0.8	23/32 (72)	26/32 (81)	0.6

Table 3 Logistic regression analyses of predictive factors associated with testosterone recovery at 12 months after brachytherapy before and after propensity score matching

	Univariate odds ratio (95%CI)	*P*-value	Multivariate odds ratio (95%CI)	*P*-value	Multivariate (PS matching) odds ratio (95%CI)	*P*-value
Age	0.87 (0.783–0.967)	0.01	0.885 (0.783–1.00)	0.051	0.794 (0.639–0.988)	0.04
BMI	0.842 (0.72–0.983)	0.03	0.857 (0.722–1.02)	0.077	0.736 (0.55–0.986)	0.04
Initial PSA level	0.985 (0.869–1.12)	0.8				
T stage	0.861 (0.497–1.49)	0.6				
Gleason grade	0.844 (0.332–2.15)	0.7				
NCCN risk group	1.31 (0.514–3.33)	0.6				
GnRH antagonist vs agonist	1.57 (0.586–4.21)	0.4	1.26 (0.437–3.63)	0.7	3.68 (0.738–19.4)	0.1
Hypertension	0.417 (0.162–1.07)	0.07	0.603 (0.218–1.67)	0.3	0.341 (0.133–1.74)	0.2
Diabetes	0.296 (0.093–0.949)	0.04	0.73 (0.181–2.94)	0.3	1.13 (0.067–9.68)	0.9
Combination with anti-androgen	2.05 (0.243–17.3)	0.5				

BMI, body mass index; NCCN, national comprehensive cancer network; PSA, prostate specific antigen.

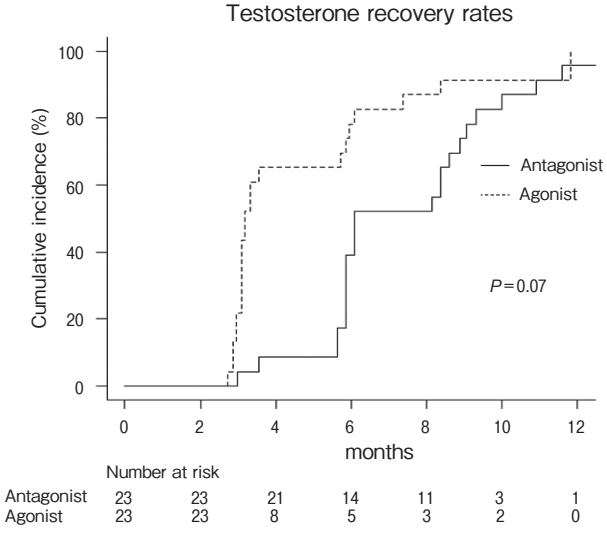

Fig. 2 Cumulative rate of recovery to normal testosterone levels after treatment with a GnRH antagonist or agonists.

dose–volume histogram cannot be determined due to pubic arch interference, a 3-month NHT regimen is generally administered. Our present study's analyses revealed no significant difference in prostate volume reduction between the patients treated with a GnRH antagonist and those treated with GnRH agonists. This finding is consistent with that of Axcrona *et al.*, who performed a randomized controlled trial in 179 patients treated with NHT for 12 weeks prior to definitive treatment [17]. They also reported that degarelix was non-inferior to goserelin in terms of prostate volume reduction.

The use of ADT can cause adverse events such as fatigue, decreased sexual function, hot flushes, and most importantly CVDs, which is due mainly to testosterone suppression [18,19]. Some studies demonstrated that lower testosterone levels were correlated with the increased risk of CVDs and mortality [20,21]. Androgens induce vascular-protective effects such as an attenuation of vascular inflammation and atherosclerosis as well as the promotion of the restoration of the endothelial layer [22,23]. A prolonged decrease in the testosterone level after NHT may potentially have not only physical but also psychological effects [24]. Therefore, NHT regimens that induce a rapid recovery of a patient's testosterone level should be recommended to improve the quality of life (QOL) of patients with localized prostate cancer. In the present series, the rate of testosterone recovery to a normal level was 72% in the GnRH antagonist group and 75% in the GnRH agonist group ($p=0.8$) at 12 months after brachytherapy. These results are comparable with those of previous studies [11,25,26].

The risk of hypogonadism is increased by older age,

obesity, history of hypertension, and diabetes [16]. Kato *et al.* investigated testosterone recovery according to the type of GnRH analogue used, and they reported an earlier recovery to normal testosterone levels with a GnRH antagonist compared with GnRH agonists [11]. Some studies suggested that GnRH antagonists can provide an alternative treatment to intermittent ADT [27, 28]; those authors demonstrated that for intermittent ADT, it is necessary to maintain low testosterone levels during ADT and to allow an early recovery of testosterone levels during the off-treatment period. Contrary to our hypothesis, our present findings demonstrated that the GnRH agonists induced a significantly more rapid testosterone recovery compared to the GnRH antagonist at 3 months after brachytherapy ($p < 0.0001$).

A GnRH agonist functions to overstimulate GnRH receptors, causing receptor desensitization and, consequently, a reduction of the levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Testosterone suppression is achieved after an initial LH surge, which not only delays the reduction to a castrated testosterone level but also stimulates an overproduction of testosterone [29]. Klotz *et al.* demonstrated that GnRH antagonists rapidly suppress LH and FSH levels and maintain their suppression, whereas GnRH agonists do not suppress the FSH level to the same extent as GnRH antagonists [30]. The maintained FSH function might lead to a more rapid testosterone recovery after a discontinuation of the agonist.

The propensity score analysis conducted herein revealed that the prostate cancer patients' testosterone recovery was significantly associated with age and BMI, but not with the types of GnRH analogue; these results are somewhat inconsistent with previous research [11, 31]. The median duration of NHT was 3 months in the present study versus 6 months in tis earlier research. In addition, we administered bicalutamide to only nine patients, whereas in the previous research, all of patients were administered bicalutamide. The differences in the duration of NHT and the administration rate of the anti-androgen might have led to the discrepancy in results between studies. A randomized controlled trial is underway to assess the benefit and potency of a GnRH antagonist compared with GnRH agonists as NHT before brachytherapy (UMIN000015519) [32]. We are awaiting the results of the prospective study.

There are some study limitations to address, including the relatively small sample size and retrospective design. We thus performed the propensity score matching to reduce the potential bias introduced by these limitations. Another limitation was that we could not assess the influence of the patients' pre-treatment testosterone level on testosterone recovery, as the pre-treatment testosterone levels were not available. It is possible that the more advanced stages (higher T stage and intermediate risk group) in the group of patients treated with the GnRH antagonist was a factor in the delayed testosterone recovery. In addition, the duration of NHT was prolonged in some cases if a sufficient reduction in prostate volume was not achieved; thus, the NHT duration was not equal among the study patients. Finally, we did not evaluate the detrimental physiological effects of NHT (*e.g.*, risk of CVDs) or psychological effects of NHT (*e.g.*, on QOL). Long-term follow-up is needed to determine whether differences in the duration of testosterone recovery by the types of GnRH analogue affect the risk of CVDs.

In conclusion, between the GnRH antagonist and agonists evaluated here, the GnRH agonists induced a more rapid recovery of the testosterone level after brachytherapy, with a significant difference in the testosterone recovery rate at 3 months after brachytherapy. However, there was no significant difference in testosterone recovery at 12 months between the GnRH antagonist and agonists. The testosterone recovery rate was significantly associated with older age and higher BMI. We did not observe superiority of the GnRH antagonist over the two agonists in terms of testosterone recovery. Long-term follow-up data are needed to determine the effects of testosterone recovery on the QOL of prostate cancer patients treated with brachytherapy, according to the type of GnRH analogue.

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